Mapping Cerebrovascular Reactivity Impairment in Patients With Symptomatic Unilateral Carotid Artery Disease

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Abstract: Background Comprehensive hemodynamic impairment mapping using blood oxygenation-level dependent (BOLD) cerebrovascular reactivity (CVR) can be used to identify hemodynamically relevant symptomatic unilateral carotid artery disease. Methods and Results This prospective cohort study was conducted between February 2015 and July 2020 at the Clinical Neuroscience Center of the University Hospital Zurich, Zurich, Switzerland. One hundred two patients with newly diagnosed symptomatic unilateral internal carotid artery (ICA) occlusion or with 70% to 99% ICA stenosis were included. An age-matched healthy cohort of 12 subjects underwent an identical BOLD functional magnetic resonance imaging examination. Using BOLD functional magnetic resonance imaging with a standardized CO_2 stimulus, CVR impairment was evaluated. Moreover, embolic versus hemodynamic ischemic patterns were evaluated on diffusion-weighted imaging. Sixty-seven patients had unilateral ICA occlusion and 35 patients unilateral 70% to 99% ICA stenosis. Patients with ICA occlusion exhibited lower whole-brain and ipsilateral hemisphere mean BOLD-CVR values as compared with healthy subjects (0.12±0.08 versus 0.19±0.04, P=0.004 and 0.09±0.09 versus 0.18±0.04, P<0.001) and ICA stenosis cohort (0.12±0.08 versus 0.16±0.05, P=0.01 and 0.09±0.09 versus 0.15±0.05, P=0.01); however, only 40 (58%) patients of the cohort showed significant BOLD-CVR impairment. Conversely, there was no difference in mean BOLD-CVR values between healthy patients and patients with ICA stenosis, although 5 (14%) patients with ICA stenosis showed a significant BOLD-CVR impairment. No significant BOLD-CVR difference was discernible between patients with hemodynamic ischemic infarcts versus those with embolic infarct distribution (0.11±0.08 versus 0.13±0.06, P=0.12). Conclusions Comprehensive BOLD-CVR mapping allows for identification of hemodynamically relevant symptomatic unilateral carotid artery stenosis or occlusion.

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ORIGINAL RESEARCH

Mapping Cerebrovascular Reactivity Impairment in Patients With Symptomatic Unilateral Carotid Artery Disease

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BACKGROUND: Comprehensive hemodynamic impairment mapping using blood oxygenation-level dependent (BOLD) cerebrovascular reactivity (CVR) can be used to identify hemodynamically relevant symptomatic unilateral carotid artery disease.

METHODS AND RESULTS: This prospective cohort study was conducted between February 2015 and July 2020 at the Clinical Neuroscience Center of the University Hospital Zurich, Zurich, Switzerland. One hundred two patients with newly diagnosed symptomatic unilateral internal carotid artery (ICA) occlusion or with 70% to 99% ICA stenosis were included. An age-matched healthy cohort of 12 subjects underwent an identical BOLD functional magnetic resonance imaging examination. Using BOLD functional magnetic resonance imaging with a standardized CO_2 stimulus, CVR impairment was evaluated. Moreover, embolic versus hemodynamic ischemic patterns were evaluated on diffusion-weighted imaging. Sixty-seven patients had unilateral ICA occlusion and 35 patients unilateral 70% to 99% ICA stenosis. Patients with ICA occlusion exhibited lower whole-brain and ipsilateral hemisphere mean BOLD-CVR values as compared with healthy subjects (0.12±0.08 versus 0.19±0.04, P=0.004 and 0.09±0.09 versus 0.18±0.04, P<0.001) and ICA stenosis cohort (0.12±0.08 versus 0.16±0.05, P=0.01 and 0.09±0.09 versus 0.15±0.05, P=0.01); however, only 40 (58%) patients of the cohort showed significant BOLD-CVR impairment. Conversely, there was no difference in mean BOLD-CVR values between healthy patients and patients with ICA stenosis, although 5 (14%) patients with ICA stenosis showed a significant BOLD-CVR impairment. No significant BOLD-CVR difference was discernible between patients with hemodynamic ischemic infarcts versus those with embolic infarct distribution (0.11±0.08 versus 0.13±0.06, P=0.12).

CONCLUSIONS: Comprehensive BOLD-CVR mapping allows for identification of hemodynamically relevant symptomatic unilateral carotid artery stenosis or occlusion.

Key Words: BOLD-CVR ■ hemodynamic ■ ICA occlusion ■ ICA stenosis ■ ischemic infarct

Symptomatic unilateral carotid artery disease is associated with a high risk of recurrent cerebrovascular events and poor functional outcome.[1,2] This is of particular importance considering the hemodynamic heterogeneity present in symptomatic unilateral carotid artery disease, because internal carotid artery (ICA) occlusion is commonly associated with cerebral hypoperfusion and high-grade (ie, 70%–99%) ICA stenosis with thromboembolic events, although these can even coexist.[3–5] Therefore, an imaging assessment of hemodynamic impairment is considered a better predictor than clinical scores alone, and may a better guide for clinical decision-making, including revascularization strategies.[6,7] Transcranial Doppler (TCD) is

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CLINICAL PERSPECTIVE

What Is New?

- Comprehensive blood oxygenation-level dependent cerebrovascular reactivity mapping identifies patients with hemodynamically relevant symptomatic unilateral carotid artery disease.
- The infarct pattern (hemodynamic ischemic infarcts versus embolic infarct distribution) does not significantly impact cerebrovascular reactivity in patients with symptomatic unilateral carotid artery stenosis or occlusion.

What Are the Clinical Implications?

- Blood oxygenation-level dependent cerebrovascular reactivity mapping can identify a subset of patients with severe hemodynamic impairment and can therefore support the risk-benefit evaluation of clinical management, including cerebrovascular revascularization strategies.

Nonstandard Abbreviations and Acronyms

ACA	anterior cerebral artery
ASL	arterial spin labeling
BOLD	blood oxygenation-level dependent
CVR	cerebrovascular reactivity
DWI	diffusion-weighted imaging
ICA	internal carotid artery
MCA	middle cerebral artery
NASCET	North American Symptomatic Carotid Endarterectomy Trial
PCA	posterior cerebral artery
TCD	transcranial Doppler

the most commonly used technique to evaluate intracranial flow, but has limited use in the evaluation of hemodynamic impairment, because it can only estimate brain blood flow responses by measuring major artery flow velocity.[8–10]

Mapping the perfusion reserve capacity at brain tissue level will, therefore, provide a more comprehensive assessment of hemodynamic impairment.[11–13] Although brain tissue perfusion techniques, based on single-photon emission computed tomography, positron emission tomography, and arterial spin labeling, have been widely investigated for subgroups of symptomatic carotid artery disease, none have made it into routine clinical practice. Also, to date, no reports have emerged about mapping the spectrum of hemodynamic impairment for symptomatic carotid artery disease (ie, including both unilateral occlusion and high-grade stenosis).

Blood oxygenation-level dependent (BOLD) cerebrovascular reactivity (CVR) is an emerging clinically applicable technique to evaluate hemodynamic impairment in patients with cerebrovascular steno-occlusive disease.[14–16] In this regard, BOLD-CVR may identify hemodynamically relevant symptomatic carotid artery stenosis and occlusion, because it allows for comprehensive whole-brain CVR mapping, independent of the degree of stenosis or vessel occlusion present, including detailed analyses of gray matter, white matter, and individual vascular territories.[17,18]

We hypothesized that BOLD-CVR mapping can identify impaired CVR patterns for unilateral occlusion as well as high-grade unilateral stenosis in patients with symptomatic carotid artery disease and identify patients with severe hemodynamic impairment.

METHODS

Requests to access the analysis methods and detailed results of this study may be sent to the corresponding author (M.S.).

The research ethics board of the Cantonal Ethics Committee of Zurich (KEK-ZH-Nr. 2012-0427) approved this ongoing prospective cohort study (according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[19]), which is part of an interdisciplinary BOLD-CVR project in patients with symptomatic carotid artery disease. For this cohort analysis, the subjects were selected from the period February 2015 until July 2020. Informed consent was obtained from every participant before study enrollment.

The inclusion criteria were: (1) patients aged ≥18 years with symptomatic unilateral carotid artery disease; (2) exhibiting focal neurologic symptoms that are sudden in onset and referable to the appropriate carotid artery distribution (ipsilateral to significant ICA atherosclerotic pathology), including 1 or more transient ischemic attacks, characterized by focal neurologic dysfunction or transient monocular blindness, or 1 or more minor (nondisabling) ischemic strokes[20]; and (3) either unilateral ICA occlusion or high-grade unilateral ICA stenosis of 70% to 99% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria[21] on carotid ultrasound duplex sonography. Unilateral disease was considered as a maximal stenosis of 50% on the contralateral side graded by carotid ultrasound duplex sonography according to the NASCET criteria.[21] All TCD measurements and carotid ultrasound duplex examinations

were performed clinically by an experienced vascular neurologist in the same setting.

Excluded from the study were those patients with contraindications for magnetic resonance imaging (MRI) and intolerance for the soft plastic mask or for the applied CO_2 stimulus during the BOLD-CVR examination. This was assessed under direct supervision of the subject by applying the CO_2 stimulus outside the MRI system as a test run. Also excluded were those patients with ICA dissection and bilateral carotid artery disease, which was defined as contralateral ICA stenosis >50% or a different hemodynamically relevant vascular pathology involving the contralateral ICA, such as bilateral dissection.

Twelve age-matched healthy control subjects were also recruited as a reference population (external control) to compare CVR patterns at brain tissue level. Differences in the healthy BOLD-CVR response are known and are explained by age-related changes in vascular mechanical properties[22]; therefore, we used age matching from the healthy population aged >50 years. This control group did not have a history of brain pathology, neurological disease, or neurological symptoms. These healthy control subjects underwent an identical BOLD-CVR study and signed an informed consent form before the study.

Image Acquisition and Processing

MRI data were acquired on a 3T MRI scanner (Skyra, VE11; Siemens, Erlangen, Germany) with the standard 32 channels receive-only head coil. Details of the imaging protocol and the specific analysis methods of BOLD-CVR can be reviewed in Data S1.[23–26]

Vascular Territory Analysis

Quantitative BOLD-CVR values of the major vascular territories (anterior cerebral artery, middle cerebral artery, and posterior cerebral artery territories) of ipsilateral and contralateral hemispheres were determined by applying a vascular atlas to the normalized CVR maps. This vascular atlas was derived from the predefined brain regions listed in the standard N30R83 atlas by Hammers et al[27] and Kuhn et al.[28]

Determination of Hemodynamic Versus Embolic Infarct Patterns on Diffusion-Weighted Imaging

Infarct pattern subtypes were determined as an internal consensus by an experienced board-certified stroke neuroradiologist (Dr Winklhofer), an experienced board-certified stroke neurologist (Dr Wegener), and an experienced board-certified vascular neurosurgeon (Dr Esposito) using axial diffusion-weighted imaging (DWI) volumes. Drs Winklhofer and Wegener were blinded, whereas complete blinding was not possible for Dr Esposito because of involvement in treatment of some cases.

A hemodynamic source of ischemia was classified if DWI lesions were ipsilateral to the carotid artery disease, in one vascular territory or in anterior and posterior watershed areas (with typical pearl-shaped configuration). An embolic (thromboembolic, because of carotid disease, or cardioembolic) source of ischemia was classified if single cortical–subcortical lesions or multiple lesions (eg, an embolic shower) in multiple vascular territories of the intracranial circulation to the site appropriate to ICA atherosclerotic pathology were visible.[29–32]

Statistical Analysis

We performed the statistical analysis using SPSS Statistics 26 (IBM, Armonk, NY). All continuous variables are reported as mean±SD, and dichotomous variables are shown as frequency (percent). Means of continuous variables between 2 cohorts/2 infarct pattern groups were compared by a Welch *t* test. Comparisons between BOLD-CVR values of ipsilateral and contralateral hemisphere as internal control for each cohort were made using a paired *t* test. ANOVA was used to calculate differences among the 3 groups (healthy, ICA occlusion, and ICA stenosis cohort). ANCOVA was used to statistically control the effect of covariates (age and time between neurological symptoms and BOLD-CVR investigation) for BOLD-CVR findings between ICA occlusion and ICA stenosis cohorts. $P<0.05$ was considered statistically significant.

RESULTS

Study Population Characteristics

A flowchart illustrating patient screening and inclusion can be reviewed in Figure 1. Of 150 patients screened, 102 patients met the inclusion criteria. Sixty-seven patients exhibited unilateral ICA occlusion, and 35 had high-grade unilateral ICA stenosis. Table 1 shows the relevant clinical and baseline characteristics of the enrolled patients. The median time between the neurological symptoms (transient ischemic attack, transient monocular blindness, or ischemic stroke) was 8 days (range, 1–228 days). For comparison, 12 age-matched healthy subjects were included as described above. The healthy population included right-handed nonsmokers without a history of brain pathology, neurological disease, neurological symptoms, or relevant cardiovascular pathologies. Only 1 patient had an essential hypertension, which was well controlled with an oral medication. Of the included healthy subjects,

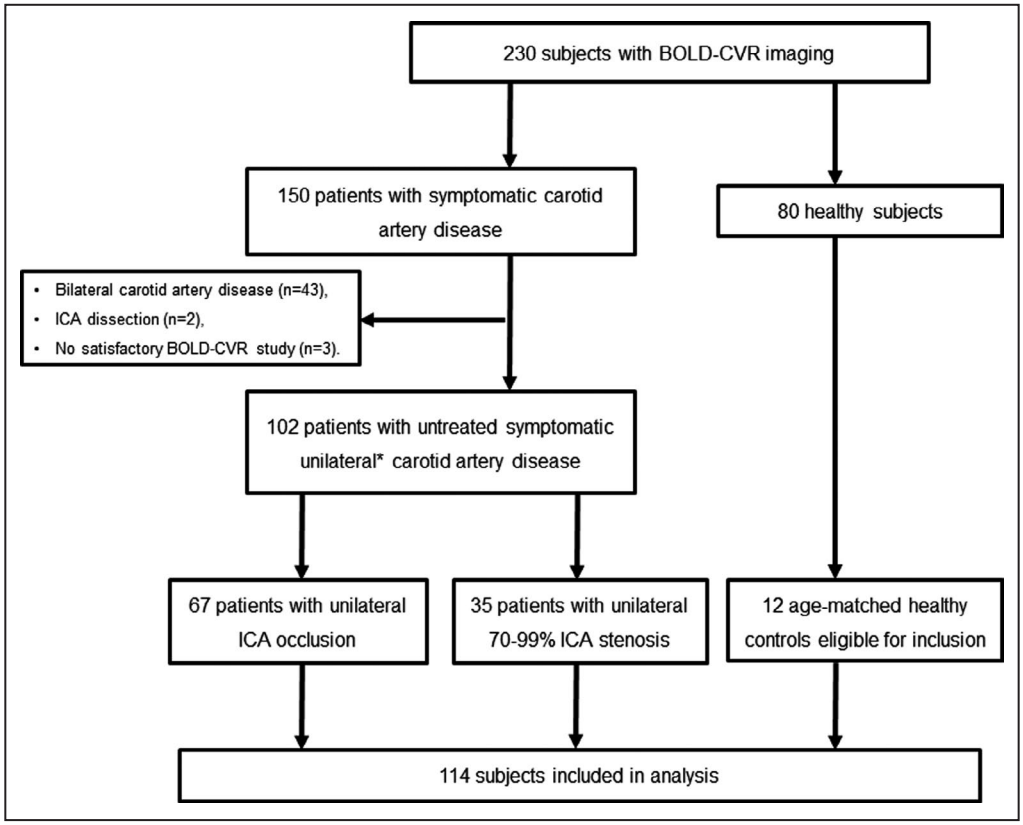

Figure 1. Study flowchart.
From the prospective database with 230 subjects who underwent blood oxygenation-level dependent (BOLD)-cerebrovascular reactivity (CVR) study, 150 patients were diagnosed with symptomatic carotid artery disease and 80 were healthy subjects. From the 150 patients with symptomatic carotid artery disease, after evaluation of exclusion criteria, 102 patients with symptomatic unilateral carotid artery disease were available for inclusion in this prospective cohort study. Patients with bilateral carotid artery disease, internal carotid artery (ICA) dissection, and without satisfactory BOLD-CVR study were excluded. Sixty-seven patients presented with unilateral ICA occlusion, and 35 patients with unilateral high-grade (70%–99%) ICA stenosis and were eligible for further analysis. Out of the 80 healthy subjects who underwent the BOLD-CVR study, we extracted 12 age-matched control subjects eligible for inclusion. In the final analysis, 114 subjects were included.

66.7% were men, and the mean age of the cohort was 65.2±9.0 years.

Cerebrovascular Reactivity Findings in Patients With Symptomatic Carotid Artery Disease

Figure 2A shows the boxplot distribution of the mean whole-brain BOLD-CVR for the 3 cohorts (ie, healthy subjects, patients with ICA occlusion, and patients with ICA stenosis) with individual patient observations. Looking ≥–2 SDs away (BOLD-CVR=0.11) from the mean whole-brain BOLD-CVR of the healthy cohort (external controls, 0.19±0.04), significant BOLD-CVR impairment (red dots) was observed in 33 (49.3%) patients with ICA occlusion and 5 (14.3%) patients with ICA stenosis. Two patients with ICA occlusion even had BOLD-CVR values of ≥+2 SDs away from the mean BOLD-CVR of the healthy cohort (0.19±0.04).

Patients with symptomatic unilateral ICA occlusion exhibited significantly impaired BOLD-CVR values for the whole brain, gray and white matter, as well as the ipsilateral and contralateral hemisphere as compared with healthy age-matched subjects (Table 2). With partial correction for age and time between neurological symptoms (stroke, transient ischemic attack, or transient monocular blindness) and BOLD-CVR investigation as possible covariates, patients with symptomatic unilateral ICA occlusion exhibited significantly impaired BOLD-CVR values for the whole brain, gray and white matter, as well as the ipsilateral hemisphere as compared with patients with symptomatic unilateral ICA stenosis (Table 2).

No difference in BOLD-CVR values between both hemispheres was seen for the healthy cohort.

Table 1. Relevant Clinical and Baseline Characteristics of Patients With Carotid Artery Disease

	ICA Occlusion, n=67	70%–99% ICA Stenosis, n=35	*P* Value
Age, y, mean±SD	64.9±11.4	71.2±7.4	0.001
Men, n (%)	53 (79.1)	30 (85.7)	0.40
Smoking, n (%)	33 (49.3)	23 (65.7)	0.11
Hypertension, n (%)	43 (64.2)	28 (80)	0.09
Hypercholesterolemia, n (%)	33 (49.3)	16 (45.7)	0.74
Obesity, n (%)	14 (20.9)	10 (28.6)	0.41
Diabetes mellitus, n (%)	12 (17.9)	5 (14.3)	0.64
Positive family history for cerebral ischemic events, n (%)	5 (7.5)	5 (14.3)	0.32

ICA indicates internal carotid artery.

Conversely, significant difference in BOLD-CVR values of ipsilateral and contralateral hemisphere is seen for both the ICA occlusion and ICA stenosis cohorts (0.09±0.09 versus 0.14±0.07, $P<0.001$ and 0.15±0.05 versus 0.17±0.05, $P<0.001$, respectively) (Table 2).

Figure 2B shows the boxplot distribution of the mean ipsilateral hemisphere BOLD-CVR for the 3 cohorts. Interestingly, looking at individual observations (dots), only 44 (43.1%) patients with symptomatic carotid artery disease showed significant (ie, ≥–2 SDs away [BOLD-CVR=0.10] from the mean ipsilateral hemisphere BOLD-CVR of the healthy cohort [0.18±0.04]), marked with red dots: 39 (58.2%) patients from the ICA occlusion and 5 (14.3%) patients from the ICA stenosis cohort. Four patients (3 with ICA occlusion and 1 with ICA stenosis) had BOLD-CVR values of ≥+2 SDs away from the mean ipsilateral BOLD-CVR of the healthy cohort (0.18±0.04).

Conversely, patients with high-grade ICA stenosis (70%–99%) as a cohort did not exhibit significant differences in mean CVR values as compared with the healthy cohort (Table 2); however, 5 (14.3%) did show significant BOLD-CVR impairment, 3 patients with 70% ICA stenosis, 1 patient with 80% ICA stenosis, and 1 patient with 90% ICA stenosis.

Among the 3 groups (healthy cohort, ICA occlusion cohort, and ICA stenosis cohort) difference in BOLD-CVR values by 1-way ANOVA was $P=0.001$ for mean CVR the whole brain and $P<0.001$ for mean CVR for the ipsilateral hemisphere.

In Figure 3, exemplary BOLD-CVR images of 2 patients with left ICA occlusion, 1 patient with 80% left ICA stenosis, 1 patient with 90% left ICA stenosis, and of a healthy subject can be reviewed. As can be appreciated in Figure 4, the degree of high-grade ICA stenosis did not have an impact either on mean whole-brain BOLD-CVR values or on mean BOLD-CVR values of ipsilateral hemisphere.

CVR Findings of Individual Vascular Territories in Patients With Symptomatic Carotid Artery Disease

Table 3 lists the CVR differences of the major vascular territories (ie, ipsilateral and contralateral, anterior cerebral artery, middle cerebral artery, and posterior cerebral artery flow territories) for the ICA occlusion versus the ICA stenosis cohort. Patients with ICA occlusion exhibited a significantly more impaired CVR of the ipsilateral anterior cerebral artery and middle cerebral artery territories as well as for the contralateral PCA territory.

Relationship Between Infarct Distribution on DWI and CVR Patterns for the Entire Cohort of Symptomatic Unilateral Carotid Disease

Out of the 102 included patients with symptomatic unilateral carotid artery disease, 24 patients had no DWI lesion. Of the 78 patients with DWI lesions present, 44 patients showed a hemodynamic infarct distribution and 34 an embolic infarct distribution (see also Methods). In the ICA occlusion cohort, 43 (64.2%) patients showed a hemodynamic infarct pattern and 12 (17.9%) patients embolic infarct distribution. Only 3 (8.6%) patients with ICA stenosis showed a hemodynamic infarct distribution, and 22 (62.9%) showed an embolic infarct pattern.

No whole-brain BOLD-CVR difference (0.11±0.08 versus 0.13±0.06, $P=0.12$) as well as no difference in the BOLD-CVR of ipsilateral hemisphere (0.08±0.09 versus 0.12±0.07, $P=0.052$) was found between patients with hemodynamic versus embolic infarct patterns. When evaluating for both groups (ICA occlusion and ICA stenosis) separately, no difference in either whole-brain BOLD-CVR or in ipsilateral hemisphere BOLD-CVR was seen.

DISCUSSION

Comprehensive BOLD-CVR imaging confirms the disseminated hemodynamic pattern known to exist for patients with unilateral symptomatic carotid artery disease and allows for identification of a subset of patients with severe hemodynamic impairment, regardless of pathogenesis of carotid artery disease.

Here, BOLD-CVR mapping shows marked CVR impairment in patients with symptomatic unilateral ICA occlusion, although only 58.2% showed true BOLD-CVR impairment, and a large spread can be seen. Interestingly, BOLD-CVR values in patients with

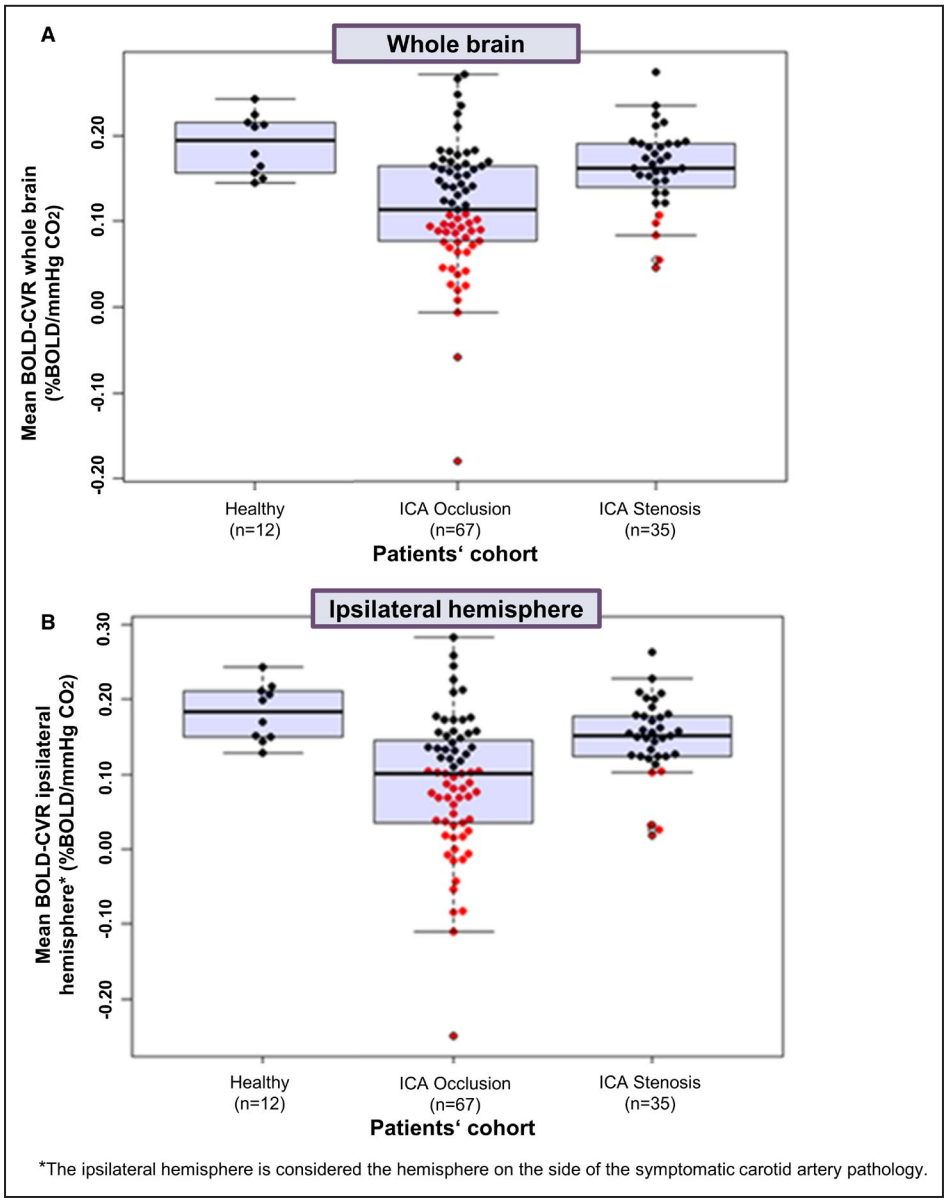

Figure 2. Distribution of mean whole-brain and mean ipsilateral hemisphere blood oxygenation-level dependent (BOLD)-cerebrovascular reactivity (CVR) values for patients with unilateral symptomatic carotid artery occlusion, unilateral symptomatic >70% carotid artery stenosis, and healthy subjects.

A, Box-whisker plots show the distribution of the whole-brain BOLD-CVR values for the 3 cohorts (ie, healthy subjects, patients with internal carotid artery (ICA) occlusion, and patients with ICA stenosis) with individual patient observations (red and black dots). Red dots represent significant BOLD-CVR impairment showing BOLD-CVR values that are ≥−2 SDs away from the mean whole-brain BOLD-CVR of the healthy cohort (BOLD-CVR=0.11). Thirty-three (49.3%) patients with ICA occlusion and 5 (14.3%) patients with ICA stenosis exhibit significant BOLD-CVR impairment. **B**, Box-whisker plots show the distribution of the ipsilateral hemisphere BOLD-CVR values for the 3 cohorts (ie, healthy subjects, patients with ICA occlusion, and patients with ICA stenosis) with individual patient observations (red and black dots). Significant BOLD-CVR impairment of ipsilateral hemisphere (red dots) was observed in 39 (58.2%) patients with ICA occlusion and in 5 (14.3%) patients with ICA stenosis. The box of the box-whisker plots represents the median value with interquartile range (25th–75th percentile). The upper and lower whiskers represent values outside the middle 50% (ie, the values below the 25th and above the 75th percentile).

Table 2. BOLD-CVR Values of Patients With Symptomatic Unilateral Carotid Artery Disease and Healthy Age-Matched Control Subjects

	Healthy Cohort, n=12	ICA Occlusion Cohort, n=67	ICA Stenosis Cohort, n=35	*P* Value Healthy vs Occlusion	*P* Value Healthy vs Stenosis	*P* Value Occlusion vs Stenosis
Mean CVR whole brain	0.19±0.04	0.12±0.08	0.16±0.05	0.004	0.54	0.01*
Mean CVR gray matter	0.22±0.04	0.13±0.08	0.18±0.05	0.007	0.53	0.02*
Mean CVR white matter	0.13±0.02	0.08±0.07	0.12±0.04	0.001	0.73	0.01*
Mean CVR ipsilateral hemisphere†,‡	0.18±0.04	0.09±0.09	0.15±0.05	<0.001	0.29	0.01*
Mean CVR contralateral hemisphere†,‡	0.19±0.04	0.14±0.07	0.17±0.05	0.11	0.82	0.09*

BOLD indicates blood oxygenation-level dependent; CVR, cerebrovascular reactivity, defined as percentage BOLD signal change per mm Hg CO_2; and ICA, internal carotid artery.

*Using ANCOVA corrected for age and time between neurological symptoms (ischemic stroke, transient ischemic attack, or transient monocular blindness) and BOLD-CVR investigation as possible covariates.

†For the healthy cohort, the right hemisphere was defined as affected and the left hemisphere as unaffected.

‡The ipsilateral hemisphere is considered the hemisphere on the side of the symptomatic carotid artery pathology.

symptomatic unilateral high-grade (70%–99%) ICA stenosis did not significantly differ from the age-matched reference healthy population; however, 5 (14.3%) patients did show a significant BOLD-CVR impairment. Furthermore, for patients with symptomatic unilateral carotid artery disease, the distribution of ischemic lesions on DWI (ie, embolic versus hemodynamic ischemic lesions) does not result in different BOLD-CVR patterns and can, therefore, not be used as a marker for hemodynamic impairment.

Contemporary Hemodynamic Imaging Approaches for Symptomatic Carotid Artery Disease

A recent review article by Derdeyn[7] provides a comprehensive overview of the current status of hemodynamic imaging in patients with chronic cerebrovascular steno-occlusive disease and lays out the 3 most important and relevant imaging parameters to assess hemodynamic impairment: oxygen extraction fraction, mean transit time, and vasodilatory capacity. BOLD-CVR would fit the latter category and has been validated against Diamox-challenged ($_{15}O$-)[H_2O]-positron emission tomography perfusion reserve measurements, where good agreement was found for staging hemodynamic failure.[14,33] In this context, BOLD-CVR imaging should be considered an alternative approach for a comprehensive and routine hemodynamic assessment in patients with carotid artery disease. In general, there is consensus that, although PET and SPECT perfusion reserve capacity imaging remain the gold-standard techniques, their current role is predominantly the validation of emerging MRI techniques that have the potential for a more cost-efficient and routine imaging approach of hemodynamic impairment mapping in patients with carotid artery disease.

Emerging MRI techniques include arterial spin labeling, where continuing methodological advances are putting this technique on the brink of routine clinical application to assess hemodynamic impairment in patients with symptomatic carotid artery disease.[34] Another recent study describes an advanced multiparametric MRI-based perfusion and oxygenation-sensitive approach.[35] Albeit, in asymptomatic carotid artery patients, such an approach is of great interest because it not only investigates blood flow impairment but also incorporates potential metabolic downregulation in chronic carotid artery disease.[36]

Other than for the established comprehensive TCD screening of stroke risk in patients with carotid artery disease, the abovementioned advanced MRI techniques, in particular BOLD-CVR, may provide more comprehensive hemodynamic information at brain tissue level, including separate analyses of gray matter, white matter, and individual vascular territories.[8]

CVR in Patients With Carotid Artery Disease: ICA Occlusion Versus ICA Stenosis

Whereas patients with ICA occlusion exhibited significantly lower mean BOLD-CVR values when being compared with the age-matched healthy cohort, patients with high-grade stenosis have mean CVR values approaching the healthy cohort. In patients with ICA occlusion, a compromised hemodynamic status is expected caused by hypoperfusion[3] but is only seen in

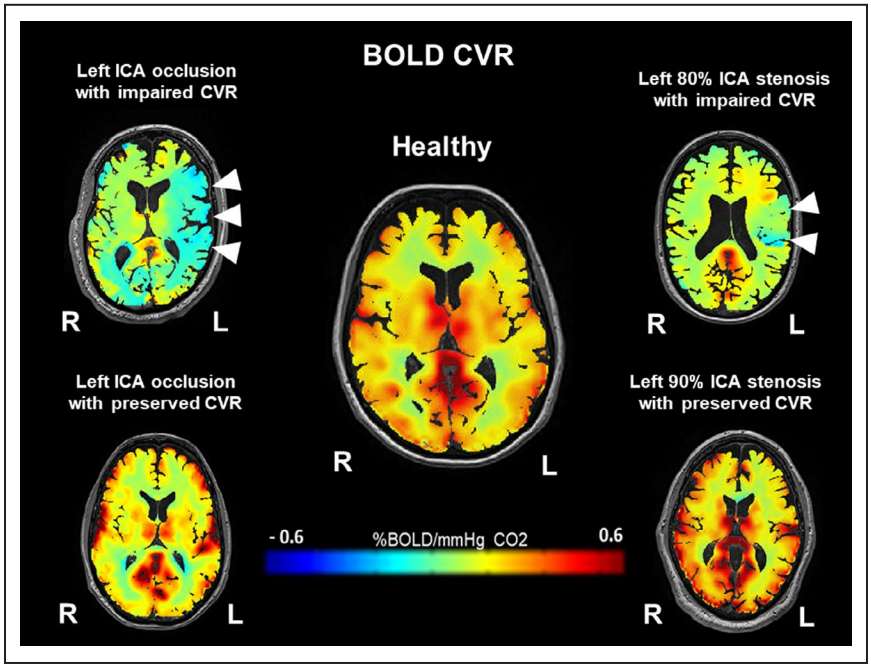

Figure 3. Exemplary blood oxygenation-level dependent (BOLD)-cerebrovascular reactivity (CVR) images of 2 patients with left internal carotid artery (ICA) occlusion, 1 healthy subject, and 2 patients with left ICA stenosis as examples for disseminated hemodynamic patterns in unilateral symptomatic carotid artery disease.
The first patient with left ICA occlusion (left upper corner of the figure) exhibits an impaired (negative) CVR in the left middle cerebral artery (MCA) territory (white triangles) as well as a negative CVR in the deep white matter of the posterior MCA territory on the right side. Conversely, the second patient with left ICA occlusion (left bottom corner of the figure) shows bilateral symmetrical CVR with especially preserved CVR in the hemisphere ipsilateral to the occluded ICA (ie, left hemisphere). In the middle of the figure, an exemplary BOLD-CVR map of a healthy subject without history of brain pathology is demonstrated. The first patient with symptomatic high-grade left ICA stenosis (80% according to NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria; right upper corner of the figure) shows impaired (negative) CVR in the left MCA territory (white triangles). For comparison, the patient with 90% ICA stenosis on the right bottom corner of the figure has preserved CVR.

58% of patients. In contrast, in patients with symptomatic high-grade stenosis, the predominant mechanism is considered to be thromboembolic, and only 14% patients showed significant BOLD-CVR impairment.[4,37] It is known that the presence of arterial stenosis or occlusion does not always match the degree of hemodynamic impairment. For instance, up to 50% of patients with complete ICA occlusion and prior ischemic symptoms have normal cerebral hemodynamics, which is in line with our findings.[38] The adequacy of collateral flow is, therefore, a determining factor for the development of a stroke.[39,40] Accordingly, BOLD-CVR findings can be an indicator to identify hemodynamically relevant symptomatic patients with carotid artery disease who need a further clinical workup. Here, TCD can be performed in a complementary fashion, supporting BOLD-CVR, to assess the collateral flow activation, the plaque morphology, and thromboembolic risk.

Impact of Infarct Distribution on CVR

The heterogeneity of infarct distribution on DWI in our patient cohort confirms the postulated hypothesis that embolism and hypoperfusion play a synergetic role,[41] and that the ischemic pattern does not always match the patients' hemodynamic status.[42] Although our carotid artery occlusion cohort did not show differences in BOLD-CVR values, we have to be aware of a small subgroup with an embolic pattern. A recent study[42] postulated that embolization plays a major role in the mechanism of injury in symptomatic large-vessel carotid disease, including carotid occlusion. Caplan and Hennerici[5] postulated an interesting link between hypoperfusion, embolism, and ischemic stroke in extracranial and intracranial occlusive vascular disease. They proposed that reduced perfusion limits the ability of the bloodstream to wash out emboli and that it thus supports infarctions, especially in the brain border zones.

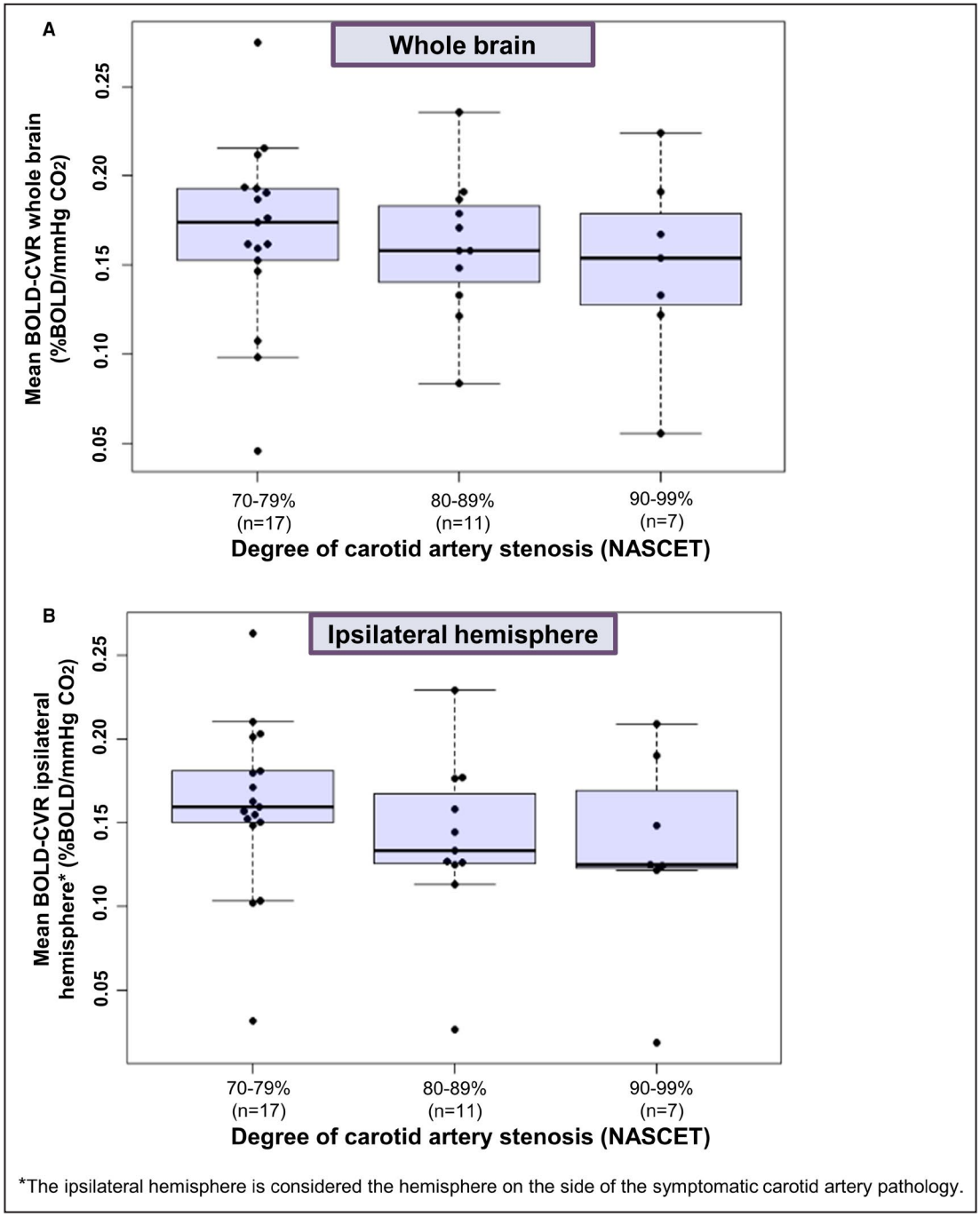

Figure 4. Correlation of internal carotid artery (ICA) stenosis degree with mean whole-brain and mean ipsilateral hemisphere blood oxygenation-level dependent (BOLD)-cerebrovascular reactivity (CVR) values.

A, Box-whisker plots show the correlation between the degree of symptomatic carotid artery stenosis according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria and BOLD-CVR values of the whole brain with individual patient observations (black dots). No differences in BOLD-CVR values are observed between patients with 70% to 79%, 80% to 89%, and 90% to 99% ICA stenosis. **B**, Box-whisker plots show the correlation between the degree of symptomatic carotid artery stenosis according to NASCET criteria and BOLD-CVR values of ipsilateral hemisphere with individual patient observations (black dots). No differences in BOLD-CVR values are observed between patients with 70% to 79%, 80% to 89%, and 90% to 99% ICA stenosis. The box of the box-whisker plots represents the median value with interquartile range (25th–75th percentile). The upper and lower whiskers represent values outside the middle 50% (ie, the values below the 25th and above the 75th percentile).

Table 3. BOLD-CVR Values of Individual Vascular Territories in Patients With Unilateral Symptomatic Carotid Artery Disease

	ICA Occlusion Cohort, n=67	ICA Stenosis Cohort, n=35	*P* Value
ACA ipsilateral*	0.08±0.08	0.13±0.07	0.001
MCA ipsilateral*	0.06±0.09	0.13±0.08	<0.001
PCA ipsilateral*	0.23±0.14	0.25±0.16	0.49
ACA contralateral	0.13±0.07	0.15±0.07	0.17
MCA contralateral	0.14±0.08	0.16±0.06	0.11
PCA contralateral	0.23±0.10	0.28±0.13	0.06

ACA indicates anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; and PCA, posterior cerebral artery.

*The ipsilateral hemisphere is considered the hemisphere on the side of the symptomatic carotid artery pathology.

This concept supports our results that hemodynamic impairment is an existing phenomenon in patients with carotid occlusion (as observed from impaired CVR values), which analogously increases the risk for additional embolic events attributable to impaired clearance of emboli (ie, washout). Moreover, this also explains the predominantly hemodynamic infarct distribution, considering that the brain border zones are a favored destination for microemboli that are not cleared.[5,43]

The impact of high-grade ICA stenosis on cerebral hemodynamics is still debatable. Some studies found a significant correlation of hemodynamic impairment versus the degree of ICA stenosis.[44,45] For instance, a study by Lattanzi et al[46] in patients presenting with TIA and high-grade ICA stenosis showed reduced ipsilateral hemispheric CVR values, with CVR improvement occurring after revascularization. Others, similar to us, found the opposite.[47,48] Similarly, Powers et al,[48] using positron emission tomography, did not find a significant effect of degree of stenosis on cerebral hemodynamic.

Future Considerations and Clinical Implications

Because BOLD-CVR findings can identify a subset of patients with severe hemodynamic impairment, regardless of pathogenesis of carotid artery disease, a combined diagnostic workup (TCD+BOLD-CVR) may further aid in the risk-benefit evaluation of clinical management, including microneurosurgical and endovascular revascularization strategies. This includes symptomatic patients with ICA occlusion exhibiting impaired cerebrovascular reserve with steal phenomenon (ie, a paradoxical BOLD-CVR response), because those patients are believed to be at the highest risk for developing a future acute ischemic event.[49,50] Potentially even more important is the subgroup of symptomatic patients with ICA stenosis that also show impaired cerebrovascular reserve with steal phenomenon (on BOLD-CVR). This not only indicates that these patients are at high risk for recurrent stroke, in addition, the presence of steal phenomenon may also increase the risk of embolic infarctions arising from the carotid plaque. It has been postulated by others that the resulting hypoperfusion leads to less washout of emboli.[5] For those patients, a carotid endarterectomy or an endovascular procedure should be strongly considered.

Limitations

The study represents single-center–based findings in a cohort of patients with symptomatic unilateral carotid disease. The study cohort was taken from a selected time period of an ongoing prospective study on BOLD-CVR in patients with symptomatic carotid artery disease and may have resulted in an underrepresentation of patient subgroups. In particular, patients presenting symptomatic unilateral high-grade ICA stenosis who are selected for carotid endarterectomy are usually scheduled for surgery within 72 hours at our institution, thereby limiting these patients for partaking in a research study. A selection bias was introduced to the study because symptomatic patients with suspected hemodynamic impairment underwent a BOLD-CVR examination. We included only 12 age-matched healthy subjects to stay as close to the age of the carotid disease population as possible. Differences in the healthy BOLD-CVR response are known and are explained by age-related changes in vascular mechanical properties.[22] Furthermore, to determine the BOLD-CVR values of vascular territories, we used an atlas-based calculation of anterior cerebral artery, middle cerebral artery, and posterior cerebral artery territories; however, the size and geometry of territories can vary between included subjects.

CONCLUSIONS

Comprehensive BOLD-CVR mapping allows for identification of hemodynamically relevant symptomatic unilateral carotid artery stenosis or occlusion.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

MRI data were acquired on a 3-tesla Skyra VD13 (Siemens Healthineers, Forchheim, Germany) with a 32-channel head coil. BOLD fMRI parameters and a three dimensional (3D) T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) image was performed according to the method similar to our previous published work.

During the BOLD fMRI sequence, the standardized carbon dioxide stimulus was applied by a computer controlled gas blender with prospective gas targeting algorithms (RespirAct^{TM}, Thornhill Research Institute, Toronto, Canada). The RespirAct^{TM} allows for precise targeting of arterial partial pressure CO_2 while maintaining normal levels of O_2 (iso-oxia).

All the acquired raw BOLD fMRI volumes were transferred to an external computer and pre-processed with SPM 12 (Statistical Parameter Mapping Software, Wellcome Department of Imaging Neuroscience, University College of London, London, UK). The BOLD fMRI volumes were processed and aligned to the T1-weighted MP RAGE image and normalized in Montreal Neurological Institute (MNI) Space as well as smoothed with a Gaussian Kernel (for more information, see Sebök et al. 2018, Methods).

The CVR calculations were done according to our previously communicated analysis pipeline. In brief, the analysis included a voxel-wise temporal shifting for optimal physiological correlation of the BOLD signal and CO_2 time series. CVR, defined as the percentage of BOLD signal change /mmHg CO_2, was then calculated from the slope of a linear least square fit of the BOLD signal time course to the CO_2 time series over the range of the first baseline of 100 seconds, the step portion of the protocol (80 seconds) and the second baseline of 100 seconds on a voxel-by-voxel basis. Baseline was deemed the subject's own

resting CO_2. The additional BOLD fMRI volumes were acquired to allow for potential temporal shift.